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(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING DRUGS WHICH ARE INSTABLE OR SPARINGLY SOLUBLE IN WATER AND METHODS FOR THEIR PREPARATION

(57) Abstract

Novel pharmaceutical compositions comprise inclusion compounds of drugs, which are instable or only sparingly soluble in water, with partially etherified β-cyclodextrin derivatives having hydroxyalkyl and optionally additional alkyl groups.

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Pharmaceutical compositions containing drugs which are instable or sparingly soluble in water and methods for their preparation

The invention relates to pharmaceutical compositions containing drugs which are instable or only sparingly soluble in water, and methods for their preparation. The compositions are characterized by increased water solubility and improved stability.

A large number of drugs is only poorly or sparingly soluble in water so that suitable application forms like drop solutions or injection solutions are being prepared using other polar additives like propylene glycol etc. If the drug molecule has basic or acidic groups there exists the further possibility of increasing the water solubility by salt formation. As a rule this results in decreased efficacy or impaired chemical stability. Due to the shifted distribution equilibrium the drug may penetrate the lipophilic membrane only slowly corresponding to the concentration of the non-dissociated fraction while the ionic fraction may be subject to a rapid hydrolytic decomposition.

Additional "water-like" solvents like low molecular polyethylene glycols or 1,2-propylene glycol are therefore used in the preparation of aqueous solutions of sparingly water-soluble drugs which glycols, however, cannot be considered pharmacologically inert, or the drug is solubilized using surfactants so that the drug molecules are occluded in micells. This solubilization has numerous

disadvantages: The surfactant molecules used have frequently a strongly haemolytic effect and the drug needs to pass out of the micell by diffusion after the application. This results in a retard effect (compare B.W. Müller, Gelbe Reihe, Vol. X, pages 132ff (1983)).

Accordingly it may be stated that there exists no satisfactory and generally applicable method of solubilization.

For solid drugs it is also important to render the sparingly water-soluble drug water-soluble since a good solubility increases the bioavailability of the drug. It has been described that inclusion compounds, e.g. with urea or complexes of polyvinyl pyrrolidone may improve the solubility of a compound but in aqueous solution they are not stable. Such inclusion compounds are therefore at best suitable for solid application forms of drugs.

This is different when using α-, ß-, and γ-cyclodextrin which can bind a drug in its ring also in aqueous solution (W. Sänger, Angewandte Chemie 92, 343 (1980)). However, it is disadvantageous that the ß-cyclodextrin itself is only poorly water-soluble (1.8 g/100 ml) so that the therapeutically necessary drug concentrations are not achieved.

If a derivative is formed of the cyclodextrin its solubility and therefore the amount of dissolved drug may be considerably increased. Thus, German Offenlegungsschrift 31 18 218 discloses a solubilization method using methylated ß-cyclodextrin as monomethyl derivative with 7 methyl groups and especially as dimethyl derivative with 14 methyl groups. With the 2,6-di-O-methyl derivative it is for instance possible to increase the water solublity of indometacin 20.4-fold and that of digitoxin 81.6-fold.

However, for therapeutical use the methyl derivatives of ß-cyclodextrin show serious draw backs. Due to their increased lipophility they have a haemolytic effect and they further cause irritations of the mucosa and eyes. Their acute intravenous toxicity is still higher than the already considerable toxicity of the unsubstituted ß-cyclodextrin. It is a further serious disadvantage for the practical application that the solubility of the dimethyl ß-cyclodextrin and its complexes suffers a steep decrease at higher temperatures so that crystalline dextrin precipitates upon heating. This phenomenon makes it very difficult to sterilize the solutions at the usual temperatures of 100 to 121°C.

Quite surprisingly it has now been found that certain other ß-cyclodextrin derivatives can form inclusion compounds which also considerably increase the water-solubility of sparingly water-soluble and instable drugs without showing the advantages described above.

Subject of the invention are therefore novel pharmaceutical compositions comprising inclusion compounds of only sparingly water-soluble and in water instable drugs with a partially etherified ß-cyclodextrin of the formula

(ß-CD)OR (I),

in which the residues R are hydroxyalkyl groups and part of the residues R may optionally be alkyl groups, the ß-cyclodextrin ether having a water-solubility of more than 1.8 g in 100 ml water.

A partially etherified ß-cyclodextrin of formula I is preferably used in which the residues R are hydroxyethyl, hydroxypropyl or dihydroxypropyl groups. Optionally part of the residues R may for instance be methyl or ethyl

groups; the use of partially methylated ß-cyclodextrin ethers with 7 to 14 methyl groups in the ß-cyclodextrin molecule, as they are known from German Offenlegungsschrift 31 18 218 do not come under the present invention. Partial ethers of ß-cyclodextrin comprising only alkyl groups (methyl, ethyl) may be suitable in accordance with the invention if they have a low degree of substitution (as defined below) of 0.05 to 0.2.

ß-cyclodextrin is a compound with ring structure consisting of 7 anhydro glucose units; it is also referred to as cycloheptaamylose. Each of the 7 glucose rings contains in 2-,3-, and 6-position three hydroxy groups which may be etherified. In the partially etherified ß-cyclodextrin derivatives used according to the invention only part of these hydroxy groups is etherified with hydroxyalkyl groups and optionally further with alkyl groups. When etherifying with hydroxy alkyl groups which can be carried out by reaction with the corresponding alkylene oxides, the degree of substitution is stated as molar substitution (MS), viz. in mole alkylene oxide per anhydroglucose unit, compare US patent specification 34 59 731, column 4. In the hydroxyalkyl ethers of ß-cyclodextrin used in accordance with the invention the molar substitution is between 0.05 and 10, preferably between 0.2 and 2. Particularly preferred is a molar substitution of about 0.25 to about 1.

The etherification with alkyl groups may be stated directly as degree of substitution (DS) per glucose unit which - as stated above - is 3 for complete substitution. Partially etherified ß-cyclodextrins are used within the invention which comprise besides hydroxyalkyl groups also alkyl groups, especially methyl or ethyl groups, up to a degree of substitution of 0.05 to 2.0, preferably 0.2 to 1.5. Most preferably the degree of substitution with alkyl groups is between about 0.5 and about 1.2.

The molar ratio of drug to ß-cyclodextrin ether is preferably about 1:6 to 4:1, especially about 1:2 to 1:1. As a rule it is preferred to use the complex forming agent in a molar excess.

Useful complex forming agents are especially the hydroxyethyl, hydroxypropyl and dihydroxypropyl ether, their corresponding mixed ethers, and further mixed ethers with methyl or ethyl groups, such as methyl-hydroxyethyl, methyl-hydroxypropyl, ethyl-hydroxyethyl and ethyl-hydroxypropyl ether of ß-cyclodextrin.

The preparation of the hydroxyalkyl ethers of ß-cyclodextrin may be carried out using the method of US patent specification 34 59 731. Suitable preparation methods for ß-cyclodextrin ethers may further be found in J. Szejtli et al., Stärke 32, 165 (1980) und A.P. Croft and R.A. Bartsch, Tetrahedron 39, 1417 (1983). Mixed ethers of ß-cyclodextrin can be prepared by reacting ß-cyclodextrin in a basic liquid reaction medium comprising an akali metal hydroxide, water and optionally at least one organic solvent (e.g. dimethoxyethane or isopropanol) with at least two different hydroxyalkylating and optionally alkylating etherifying agents (e.g. ethylene oxide, propylene oxide, methyl or ethyl chloride).

Drugs exhibiting a significantly increased water-solubility and improved stability, respectively, after having been transferred into inclusion compounds with the above-mentioned ß-cyclodextrin ethers are those having the required shape and size, i.e. which fit into the cavity of the ß-cyclodextrin ring system. This includes for instance non-steroid anti-rheumatic agents, steroids, cardiac glycosides and derivatives of benzodiazepine, benzimidazole, piperidine, piperazine, imidazole or triazole.

Useful benzimidazole derivatives are thiabendazole, fuberidazole, oxibendazole, parbendazole, cambendazole, mebendazole, fenbendazole, flubendazole, albendazole, oxfendazole, nocodazole and astemisole. Suitable piperadine derivatives are fluspirilene, pimozide, penfluridole, loperamide, astemizole, ketanserine, levocabastine, cisapride, altanserine, and ritanserine. Suitable piperazine derivatives include lidoflazine, flunarizine, mianserine, oxatomide, mioflazine and cinnarizine. Examples of suitable imidazole derivatives are metronidazole, ornidazole, ipronidazole, tinidazole, isoconazole, nimorazole, burimamide, metiamide, metomidate, enilconazole, etomidate, econazole, clotrimazole, carnidazole, cimetidine, docodazole, sulconazole, parconazole, orconazole, butoconazole, triadiminole, tioconazole, valconazole, fluotrimazole, ketoconazole, oxiconazole, lombazole, bifonazole, oxmetidine, fenticonazole and tubulazole. As suitable triazole derivatives there may be mentioned virazole, itraconazole and terconazole.

Particularly valuable pharmaceutical compositions are obtained when converting etomidate, ketoconazole, tubulazole, itraconazole, levocabastine or flunarizine into a water-soluble form using the complex forming agents of the invention. Such compositions are therefore a special subject of the present invention.

The invention is further directed to a method of preparing pharmaceutical compositions of sparingly water-soluble or water-instable drugs which is characterized by dissolving the ß-cyclodextrin ether in water and adding thereto the selected drug as well as optionally drying the solution of the formed inclusion compound using methods known per se. Formation of the solution may take place at temperatures between 15 and 35°C.

The drug is suitably added batchwise. The water may further comprise physiologically compatible compounds such as sodium chloride, potassium nitrate, glucose, mannitole, sorbitol, xylitol or buffers such as phosphate, acetate or citrate buffer.

Using ß-cyclodextrin ethers in accordance with the invention it is possible to prepare application forms of drugs for oral, parenteral or topical application, e.g. infusion and injection solutions, drop solutions (e.g. eye drops or nasal drops), sprays, aerosols, sirups, and medical baths.

The aqueous solutions may further comprise suitable physiologically compatible preserving agents such as quarternary ammonium soaps or chlorbutanol.

For the preparation of solid formulations the solutions of the inclusion compounds are dried using conventional methods; thus the water may be evaporated in a rotation evaporator or by lyophilisation. The residue is pulverized and, optionally after addition of further inert ingredients, converted into uncoated or coated tablets, suppositories, capsules, creams or ointments.

The following examples serve to illustrate the invention which, however, is not restricted to the examples.

The phosphate buffer solution mentioned in the examples had a pH of 6.6 and the following composition:

KH_2PO_4	68,05 g
NaOH	7,12 g
Aqua demin. ad.	5000,0 g

$68.05\,g \times \frac{mol}{136.09\,g} \times \frac{1}{5\,L} = 0.1\,M$

All percentages are percent by weight.

Example 1

Starting from a 7% master solution of hydroxyethyl ß-cyclodextrin (MS 0.43) in phosphate buffer solution a dilution series was prepared so that the complex forming agent concentration was increased in steps of 1%. 3 ml of these solutions were pipetted into 5 ml snap-top-glasses containing the drug to be tested. After shaking for 24 hours at 25°C the solution was filtered through a membrane filter (0.22 microns) and the dissolved drug content was determined spectrophotometrically. Figures 1, 3 and 4 show the increase of the drug concentration in solution in relation to the concentration of the complex forming agent for indometacin (figure 1), piroxicam (figure 3) and diazepam (figure 4). The maximum drug concentration is limited by the saturation solubility of the cyclodextrin derivative in the buffer which in case of hydroxyethyl-ß-cyclodextrin (MS 0.43) is reached at 7.2 g/100 ml.

When comparing for instance the results obtained with indometacin to those given in German Offenlegungsschrift 31 18 218 for 2,6-di-O-methyl-ß-cyclodextrin (figure 2) it will be observed that the hydroxyethyl derivative has a significantly higher complex formation constant (compare the different slopes in figures 1 and 2).

Example 2

A. The saturation solubility at 25°C of different drugs was determined using a 10% hydroxypropyl-ß-cyclodextrin solution (MS 0.35) in phosphate buffer solution under the same conditions as in example 1. The saturation solubilities S_1 in phosphate buffer solution and

S_2 in phosphate buffer solution and 10% added hydroxypropyl-ß-cyclodextrin are given in table 1.

Table 1

Drugs	S_1 (mg/ml)	S_2 (mg/ml)	Ratio S_1:S_2
Indometacine	0,19	5,72	1: 30,1
Digitoxine	0,002	1,685	1: 842,5
Progesterone	0,0071	7,69	1: 1083,0
Dexamethasone	0,083	14,28	1: 172,0
Hydrocortisone	0,36	21,58	1: 59,9
Diazepame	0,032	0,94	1: 29,4

B. The solubility of drugs in a 4% aqueous solution of hydroxypropyl-methyl-ß-cyclodextrin (DS 0.96; MS 0.43) was determined in a similar manner. The results obtained are summarized in the following table 2 in which the ratio R of the saturation solubility in water or at the stated pH, respectively, with an without addition of ß-cyclodextrin derivative is stated for each drug. The solutions prepared according to the invention were further found to be significantly more stable when compared with aqueous solutions.

Table 2

Drug			R
Itraconazole	at	pH 5	96
	at	pH 2,5	75
Flunarizine			18
Levocabastine	at	pH 9,5	81
	at	pH 7,4	8
Ketoconazole			85
Flubendazole			30
Tubulazole			43
Cisapride			3
Loperamide			62
Etomidate			8,5
Cinnarizine	at	pH 5	28
	at	pH 3	12

Example 3

In 10 ml phosphate buffer solution 0.7 g hydroxyethyl-ß-cyclodextrin (MS 0.43) were dissolved together with 0.04 g indometacin at 25°C until a clear solution was formed. This solution was filtered through a membrane filter (0.22 microns) and filled under laminar flow into a pre-sterilized injection bottle which was stored at 21°C (B). In a parallel test a saturated indometacin solution in a phosphate buffer solution (0.21 mg/ml) was stored under the same conditions (A). The drug concentrations determined by high pressure liquid chromatography are given in table 3. The great improved stability of the composition according to the invention is apparent.

Table 3

Storing time in weeks	Indometacin content (%) A	B
0	100,1	99,7
2	91,2	99,9
4	79,1	98,1
6	69,8	98,6
8	64,8	98,4

Example 4 (Injectable formulation)

0.35 g hydroxypropyl-ß-cyclodextrin (MS 0.35) were dissolved in 5 ml of physiological sodium chloride solution and warmed to about 35°C whereafter 3 mg diazepam were added. After storing for a short time a clear solution was obtained which was filled into an ampule after filtration through a membrane filter (0.45 microns).

Example 5 (Tablet)

In 100 ml water 7 g hydroxyethyl-ß-cyclodextrin (MS 0.43) and 0.5 g medroxyprogesterone acetate were dissolved. The water was then evaporated in a rotation evaporator. The residue (75 mg) was powdered and after addition of 366 mg calcium hydrogen phosphate.$2H_2O$, 60 mg corn starch, 120 mg cellulose powder (microcrystalline), 4.2 mg highly dispersed silica (AEROSIL^R 200) and 4.8 mg magnesium stearate tablets with a weight of 630.0 mg and comprising 5 mg drug per unit dose were made. The dissolution rate of the medroxyprogesterone acetate from this formulation is 21 times higher when compared to a tablet comprising the same inert ingredients without addition of the ß-cyclodextrin ether.

Example 6

5 g hydroxyethyl-ß-cyclodextrin (MS 0,43) and 14 mg vitamin A-acetate were dissolved with stirring in 100 ml water or sugar solution (5% aqueous solution) within 2.5 hours under a nitrogen atmosphere. After filtration through a membrane filter (0.45 microns) the solution was filled into ampules and sterilized or filled into dropper bottles with addition of 0.4% chlor butanol as preserving agent.

Example 7

5 or 7.5 g hydroxyethyl ß-cyclodextrin (MS 0.43) and 0.5 or 0.75 g Lidocaine were dissolved in 100 ml of physiological sodium chloride solution at 30°C (B). Injection solutions, eye droplets and solutions for topical use were prepared therefrom as described in example 6. When comparing the anaethesic effect of these solutions in animal tests with an aqueous lidocain HCl solution (A) one observes an extension of the duration of the effect by 300%. Test: rats, injection of 0.1 ml into the tail root in the vicinity of the right or left nerve fillaments and electrical irritation. The test results are summarized in table 4.

Table 4

Drug concentration (%)	Duration of effect (min) A	B	Extension (%)
0,5	56	163	291
0,75	118	390	330

Example 8

6 mg dexamethasone and 100 mg hydroxyethyl-ß-cyclodextrin (MS 0.43) were dissolved in 5 ml water, sterilized by filtration through a membrane filter (0.22 microns) and packed into an aerosol container allowing to dispense 0.1 ml per dose.

Example 9

The acute intravenous toxicity of some ß-cyclodextrins was tested on rats with the following results. It was surprisingly found that the toxicity of the derivatives used according to the invention is lower by an entire order of magnitude.

Table 5

	LD_{50} in rats (i.v.) in mg/kg bodyweight
ß-cyclodextrin	453
dimethyl-ß-cyclodextrin (DS 2.0)	200-207
hydroxypropyl-methyl-ß-cyclodextrin (DS 0.96; MS 0.43)	> 2000*

* a higher dose has not been tested. In mice the value was ≥ 4000 mg/kg.

The haemolytic effect of the methylether according to German Offenlegungsschrift 31 18 218 was compared to that of an ether used according to the invention. To this end 100 µl of a physiological sodium chloride solution with a cyclodextrin content of 10%, 800 µl of a buffer (400 mg MOPS, 36 mg Na_2HPO_4 . 2 H_2O, 1,6 g NaCl in 200 ml H_2O) and 100 µl of a suspension of human red blood cells (three times washed with sodium chloride solution) were mixed for 30 minutes at 37°C. Thereafter the mixture was centrifuged and the optical density was determined at 540 nm.

Controls:
a) 100 µl sodium chloride solution + buffer → 0% haemolysis
b) 900 µl water → 100% haemolysis

The results obtained are summarized in the following table 6 in which the concentrations are stated at which 50% and 100% haemolysis occurred.

Table 6

Substance	C_{50}%	C_{100}%
Dimethyl-ß-CD (DS 2.0)	0,33%	0,5%
Methyl-ß-CD (DS 1.79)	0,53	0,8%
Hydroxypropyl-methyl-ß-CD (DS 0.96; MS 0.43%)	1,5%	4 %

The results show that the haemolytic effect of the hydroxypropylmethyl ether is about 5 to 8 times weaker than that of the dimethyl ether according to the prior art. Animal tests have further shown that the hydroxyalkyl ethers do not cause irritation of the mucosa and eyes in contrast to the methyl ethers.

WE CLAIM:

1. Pharmaceutical composition comprising an inclusion compound of drugs which are instable or only sparingly soluble in water with a partially etherified ß-cyclodextrin of the formula

(ß-CD)OR (I),

in which the residues R are hydroxyalkyl groups and in which part of the residues R may optionally be alkyl groups, the ß-cyclodextrin ether having a water solubility of more than 1.8 g in 100 ml water.

2. Composition according to claim 1, characterized in that it comprises a partially etherified ß-cyclodextrin of formula I, in which the residues R are hydroxyethyl, hydroxypropyl or dihydroxypropyl groups and in which part of the residues R may optionally be methyl or ethyl groups.

3. Composition according to claims 1 or 2, characterized in that they comprise a partially etherified ß-cyclodextrin of formula I with a molar substitution by hydroxyalkyl groups of 0.05 to 10 and a degree of substitution by alkyl groups of 0.05 to 2.0.

4. Composition according to anyone of the claims 1 to 3, characterized in that it comprises the drug and the ß-cyclodextrin ether in a molar ratio of 1:6 to 4:1.

5. Composition according to anyone of claims 1 to 4, characterized in that it comprises as drug a non-steriod anti-rheumatic agent, a steroid, a cardiac glycoside or derivatives of benzodiazepine, benzimidazole, piperidine, piperazine, imidazole or triazole.

6. Composition according to anyone of claims 1 to 5, characterized in that it comprises as drug etomidate.

7. Composition according to anyone of claims 1 to 5, characterized in that it comprises as drug ketoconazole.

8. Composition according to anyone of claims 1 to 5, characterized in that it comprises as drug itraconazole.

9. Composition according to anyone of claims 1 to 5, characterized in that it comprises as drug levocabastine.

10. Composition according to anyone of claims 1 to 5, characterized in that it comprises as drug flunarizine.

11. Composition according to anyone of claims 1 to 5, characterized in that it comprises as drug tubulazole.

12. A method of preparing a pharmaceutical composition according to anyone of claims 1 to 11, characterized in that the ß-cyclodextrin ether is dissolved in water and that the selected drug is added whereafter the solution of the inclusion compound thus obtained is optionally dried using methods known per se.

13. The method of claim 12, characterized in that the residue obtained after removal of the solvent is pulverized and, optionally after addition of further inert ingredients, transferred into a solid application form.

14. The method of claims 12 or 13, characterized in that further physiologically acceptable substances are added to the water.

15. The method of claim 14 , characterized in that sodium chloride, glucose, mannitol, sorbitol, xylitol or a phosphate or citrate buffer are added to the water.

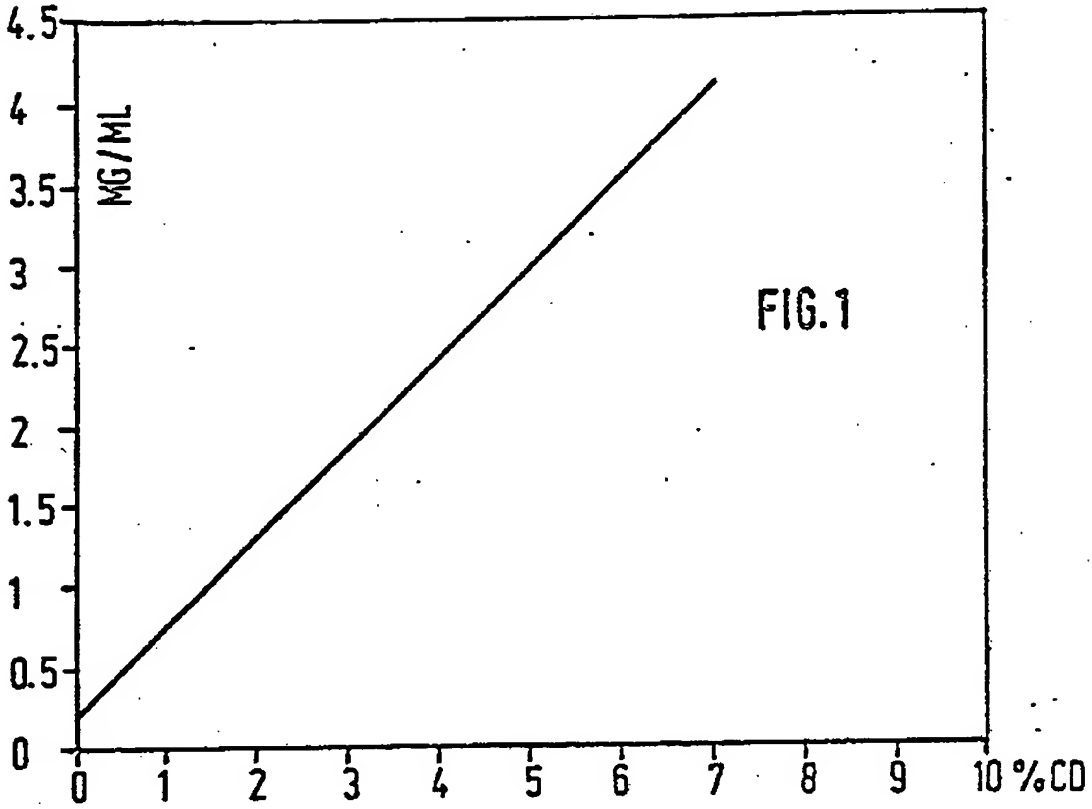
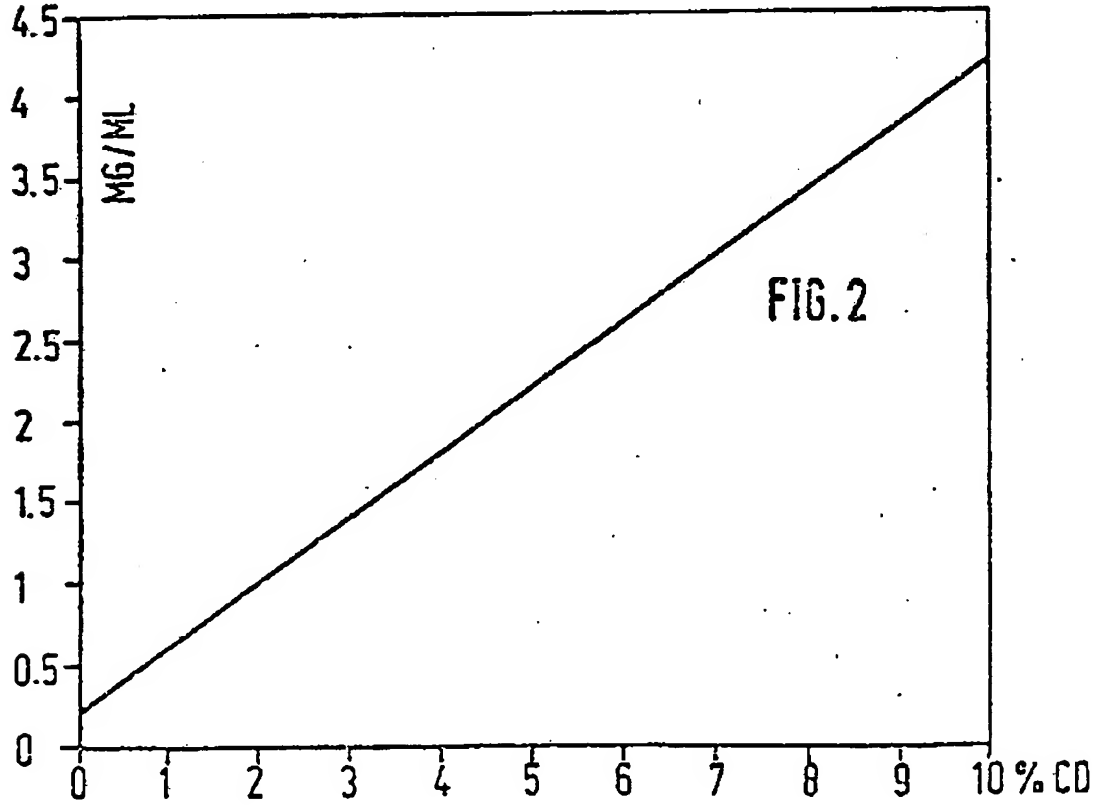

4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
MG/ML
0 1 2 3 4 5 6 7 8 9 10 %CD

FIG.1


4.5
4
3.5
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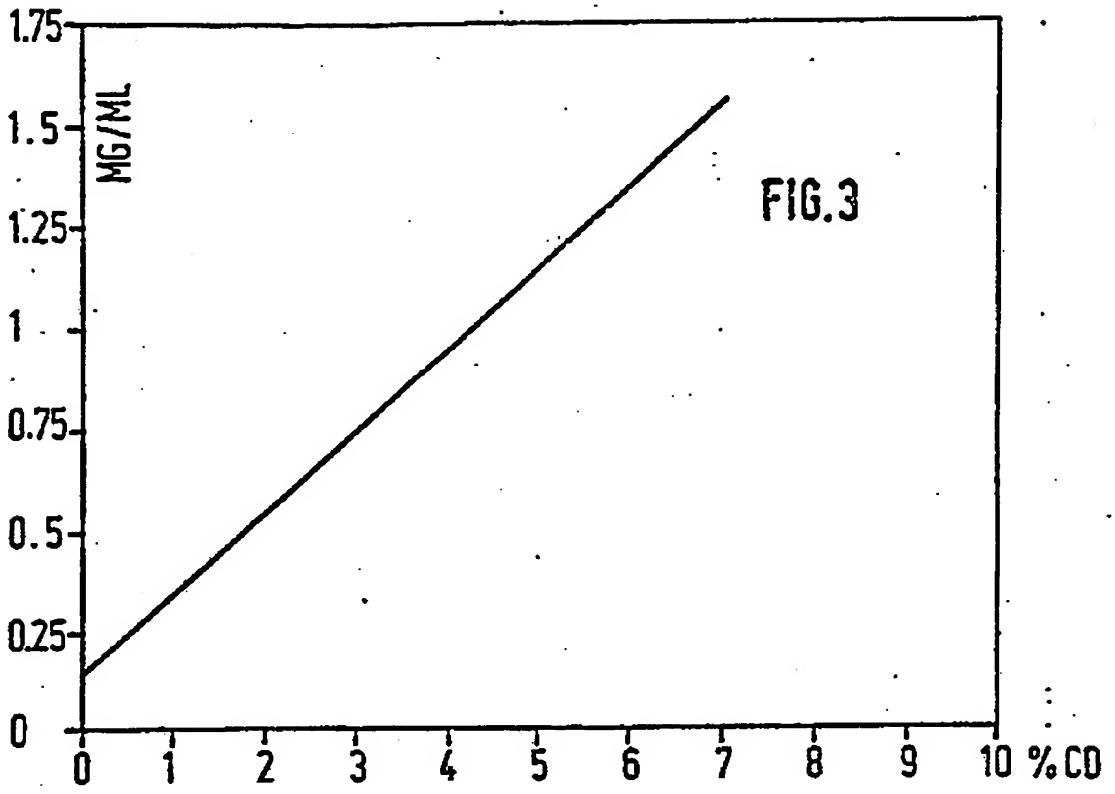
2.5
2
1.5
1
0.5
0
MG/ML
0 1 2 3 4 5 6 7 8 9 10 %CD

FIG.2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0.75
0.5
0.25
0
MG/ML
0 1 2 3 4 5 6 7 8 9 10 %CO

FIG.3

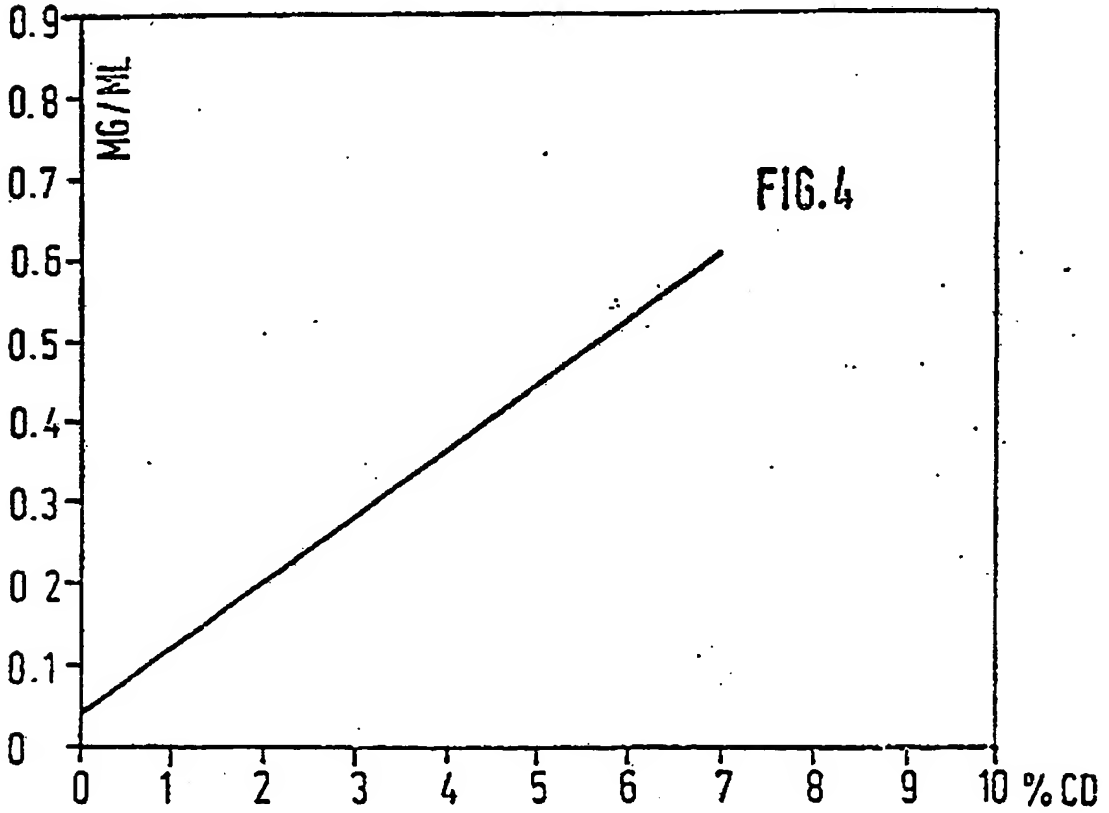
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0 2
0.1
0
MG/ML
0 1 2 3 4 5 6 7 8 9 10 %CO

FIG.4

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 84/00417

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/18; C 08 B 37/16

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K; C 08 B; C 08 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,Y	WO, A, 82/00251 (SECRETARY U.S. DEPARTMENT OF COMMERCE USA) 4 February 1982, see page 1, lines 5-17; page 10, lines 1-33; claims 2-4,8-11,21-27 --	1-5
Y	US, A, 3453259 (S.M. PARMERTER et al.) 1 July 1969, see column 1, line 1 - column 4, line 52; column 5, examples I, II; column 6, lines 26-31; claims 1,2,5,8,9 --	1-15
Y	FR, A, 1548917 (CORN PRODUCTS COMPANY) 28 October 1968, see page 5, column 1, lines 25-44; abstract A, points 1-8,10, 11 & US, A, 3459731 (cited in the application) --	1-15
Y	FR, A, 2484252 (CHINOIN GYOGYSZER-ES-VEGYESZETI TERMEKEK GYARA RT) 18 December 1981, see claims 1-8,23-34 & DE, A, 3118218 (cited in the application)	1-15

* Special categories of cited documents: [14]

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12th April 1985	10 MAI 1985
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 8400417 (SA 8555)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/05/85

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 8200251	04/02/82	EP-A-	0056056	21/07/82
		US-A-	4371673	01/02/83
		CA-A-	1175044	25/09/84
US-A- 3453259	01/07/69	None		
FR-A- 1548917	06/12/68	NL-A-	6716791	17/06/68
		US-A-	3459731	05/08/69
		GB-A-	1193197	28/05/70
		BE-A-	707947	14/06/68
FR-A- 2484252	18/12/81	BE-A-	888736	28/08/81
		DE-A-	3118218	22/04/82